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Synthesis and Molecular Structure of Di(4-hydroxy-2,6-diisoborn-2-ylphenyl)methane

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Abstract—Di(4-hydroxy-2-{(1*R**,2*S**,4*S**)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl}-6-{(1*S**,2*R**,4*R**)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl})methane was synthesized by condensation of the *meso*-diastereomer of 2,6-diisobornylphenol with paraformaldehyde under acid catalysis. The product structure as a *meso*-forms was confirmed by XRD analysis.

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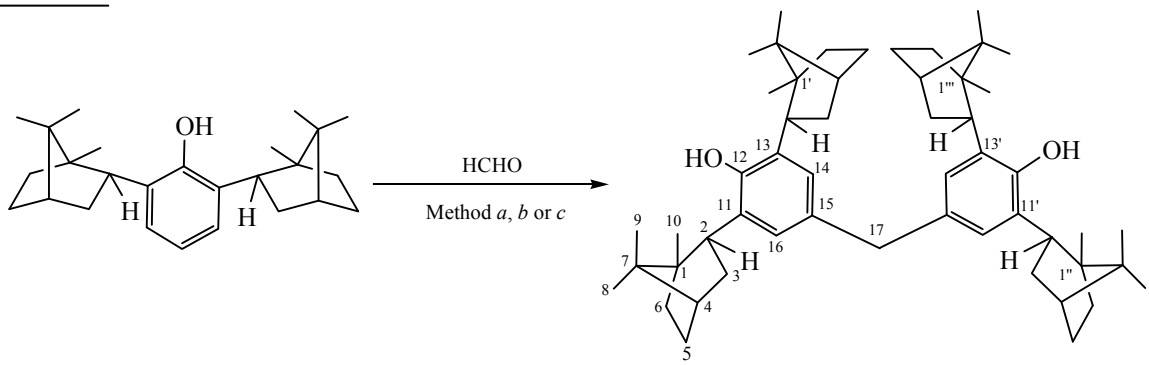
It is known that 2,2'- and 4,4'-dihydroxydiphenylmethanes (methylenebisphenols) are effective antioxidants and stabilizers of the polymeric materials [1, 2]. We have previously shown that phenols with terpene fragments and some their derivatives exhibit antioxidant properties due to the bulky terpene fragments [3, 4]. Therefore, the methyl-enebisphenols containing in the molecule the bulky isobornyl substituents are of interest for the study of their antioxidant activity.

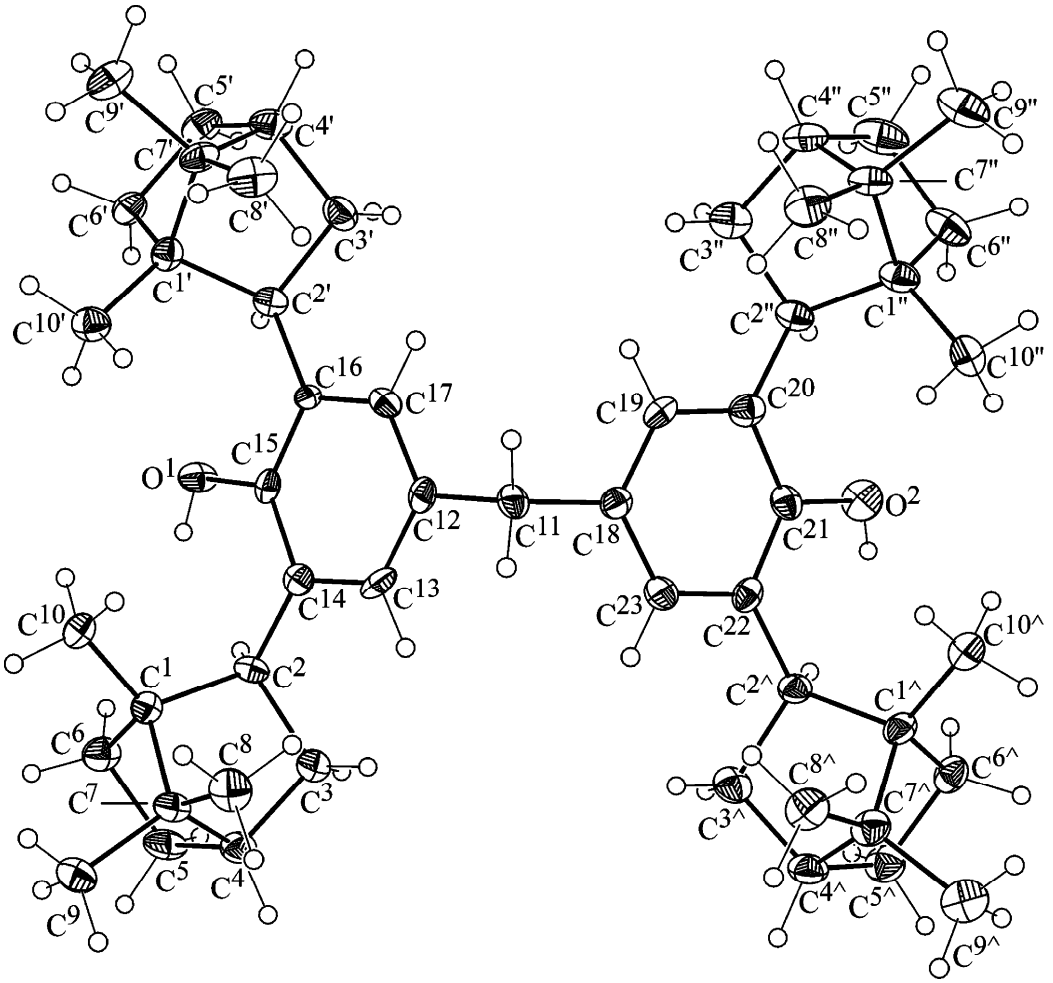
For the synthesis of 4,4'-dihydroxydiphenylmethane containing isobornyl fragments, we used a condensation of *meso*-diastereomer of 2,6-diisobornylphenol (**I**) with paraform-aldehyde, using montmorillonite KSF clay as an acid catalyst, by boiling the reagents under reflux (method *a*) or in a small steel autoclave (method *b*) [5], but the phenol **I** conversion was only 30–34%. Thus, a low conversion, despite fairly good yield, did not allow us to use these methods for preparative synthesis of di(4-hydroxy-2,6-diisoborn-2-ylphenyl)-methane (**II**). But we succeeded to increase the conversion of phenol **I** to 76% and preparative yield of the desired product **II** to 84% performing the reaction in boiling formic acid (method *c*) [1].

The numbering of carbon atoms is used to simplify analysis of NMR spectra.

Compound **II** is a colorless or light yellow powder, soluble in benzene, toluene, dimethyl sulfoxide, and diethyl ether; soluble at heating in chloroform and methylene chloride, poorly soluble in petroleum ether. The structure of compound **II** was established using IR, ^{1}H, and ^{13}C NMR spectroscopy, and elemental



meso-**I** *meso*-**II**



General view of molecule **II** at the representation of the atoms by the ellipsoids of atomic displacement with 50% probability.

analysis. In the ^{1}H and ^{13}C NMR spectra there is a set of signals characteristic of terpenophenolic fragment and of the methylene bridge. The integral intensity of the signals in the ^{1}H NMR spectrum confirms the formation of methylenebisphenol. The formation of only one diastereomer is confirmed by the presence of a single set of signals in the ^{1}H and ^{13}C NMR spectra of the compound. In the ^{1}H NMR spectra of compound **II** from the solutions in $CDCl_3$ or C_6D_6 the protons of the CH_2 group linking the two terpenophenolic fragments give a singlet (δ ~3.8 ppm), which indicates their magnetic equivalence. Previously, we have registered the equivalence of these protons in the spectra of the racemic 6,6'-methylenebis(2-isobornylphenol) [6], in accordance with the known method of the identification of diastereomers of compounds such as R*CH_2R* with the groups R* containing asymmetric centers [7]. For a reliable determination of the geometry and chirality of compound **II** we prepared its single crystals by crystallization from chloroform appropriate for the XRD analysis.

Compound **II** crystallizes in the centrosymmetric space group $P2_1/n$. A symmetrically independent part of the unit cell contains a molecule of **II** (see the figure) and two solvent molecules. Both the hydroxy groups lie in the planes of the phenyl rings. All four isobornyl substituents are oriented approximately similar with respect to the phenyl rings. A similar orientation occurred also in the previously investigated derivatives of *ortho*-isobornylphenols [4, 8, 9]. According to quantum-chemical calculations [9], such orientation is close to the most favorable in energy for the model compound, the *ortho*-isobornylbenzene. The torsion angles defining their relative orientation, $C^3C^2C^{14}C^{13}$, $C^{3'}C^{2'}C^{16}C^{17}$, $C^{3'}C^{2'}C^{20}C^{19}$, and $C^{3^\wedge}C^{2^\wedge}C^{22}C^{23}$ are –23.8(6)°, 23.4(6)°, –18.1(7)°, and 20.5(7)°, respec-

tively. The data on the relative configuration of chiral centers (1*R*,2*S*,4*S*,1'*S*,2'*R*,4'*R*,1"*R*,2"*S*,4"*S*,1'"*S*,2'"*R*,4'"*R*) of the isobornyl fragments of compound **II** obtained by X-ray diffraction study confirm the formation of *meso*-form.

Thus, starting from *meso*-diastereomer of 2,6-diisobornylphenol and paraformaldehyde we synthesized under acid catalysis di(4-hydroxy-2,6-diisoborn-2-ylphenyl)methane. Study by XRD of its geometry showed that the reaction results in the stereoselective formation of the *meso*-form.

EXPERIMENTAL

IR spectra were recorded on a Shimadzu IR Prestige 21 FT-IR spectrometer from the KBr tablets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II 300 instrument (300 and 75 MHz respectively) using solutions in $CDCl_3$ or C_6D_6. The signals assignment is based on the two-dimensional spectra (HSQC). Melting points were determined on a Koeffler hot stage. Monitoring the reaction progress was carried out by TLC on Sorbfil plates, eluent petroleum ether–Et_2O, 75:1; R_f (**I**) = 0.66, R_f (**II**) = 0.51. To detect a substance, the plates were treated with a solution containing 15 g of $KMnO_4$, 300 ml of H_2O, and 0.5 ml of conc. H_2SO_4. For column chromatography silica gel 70/230 μm of Alfa Aesar production (charging by "wet" method). Freshly distilled *n*-octane was used. For the synthesis paraformaldehyde of the chemically pure grade and formic acid of pure grade were used without further purification. Montmorillonite KSF (Alfa Aesar) was used without a preliminary treatment. *meso*-2,6-Diisoborn-2-ylphenol (*meso*-**I**) was isolated from the reaction products after alkylating phenol with camphene [10].

Di(4-hydroxy-2,6-diisoborn-2-ylphenyl)methane (II). Method *a* 0.82 mmol (0.3 g) of phenol *meso*-**I,** was dissolved in 7 ml of *n*-octane at room temperature, 0.98 mmol (0.03 g) of paraformaldehyde and 0.6 g of montmorillonite KSF was added. The reaction mixture was refluxed for 6 h adding every 1.5 h 0.49 mmol (0.03 g) of paraformaldehyde. Then the clay was filtered off and washed with chloroform, the solution was eva-porated under a reduced pressure, and the mixture obtained was separated by column chromatography on silica gel, eluent petroleum ether–Et_2O, 100:0 → 100:0.75; the mixture was preliminary dissolved in a small amount of chloroform at heating). From the reaction mixture 0.198 g of starting phenol **I** (conversion 34%) and 0.094 g of compound **II** was isolated (yield 91%, taking into account the conversion).

Method *b*. A 17 ml small steel autoclave was charged with 0.55 mmol (0.2 g) of the phenol *meso*-**I**, 0.66 mmol (0.02 g) of paraformaldehyde, 9 ml of *n*-octane, and 0.4 g of montmorillonite KSF. The reactor was heated while stirring in a glycerol bath at 130–138°C for 7 h. Then the autoclave was cooled to room temperature and opened. Further processing of the reaction mixture and separation of the reaction product were carried out by the procedure described in method *a*. From the reaction mixture 0.139 g of starting phenol **I** (conversion 30%) and 0.045 g of product **II** was isolated (yield 73%, taking into account the conversion).

Method *c*. A mixture of 1.36 mmol (0.5 g) of phenol *meso*-**I**, 1.36 mmol (0.041 g) of paraformaldehyde, and 39.8 mmol (1.5 ml) of formic acid was refluxed for 2.5 h. After cooling 5 ml of water was added, the precipitate formed was filtered off, washed with water (2×5 ml), dried, and components were separated by column chromatography similar to method *a*. 0.121 g of starting phenol **I** (conversion 76%) and 0.326 g of the product *meso*-**II** was isolated (yield 84%, taking into account the conversion).

Di(4-hydroxy-2-{(1*R,2*S**,4*S**)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl}-6-{(1*S**,2*R**,4*R**)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl})methane *meso*-II**. Colorless powder, mp 174–176°C. IR spectrum, ν, cm^{-1}: 3607, 3443 (OH), 1184 (C–O), 2949, 2876, 1458 (Me, CH_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.77 s (12H, $C^{10}H_3$, $C^{10'}H_3$, $C^{10''}H_3$, $C^{10'''}H_3$), 0.76 and 0.82, both s (12H, C^8H_3, $C^{8'}H_3$, $C^{8''}H_3$, $C^{8'''}H_3$, C^9H_3, $C^{9'}H_3$, $C^{9''}H_3$, $C^{9'''}H_3$), 1.27–1.43 m (8H, H^5, $H^{5'}$, $H^{5''}$, $H^{5'''}$, H^6, $H^{6'}$, $H^{6''}$, $H^{6'''}$), 1.49–1.67 m (8H, H^3, $H^{3'}$, $H^{3''}$, $H^{3'''}$, H^6, $H^{6'}$, $H^{6''}$, $H^{6'''}$), 1.81–1.86 m (8H, H^4, $H^{4'}$, $H^{4''}$, $H^{4'''}$, H^5, $H^{5'}$, $H^{5''}$, $H^{5'''}$), 2.13–2.19 m (4H, H^3, $H^{3'}$, $H^{3''}$, $H^{3'''}$), 2.96 t (4H, *J* 8.6 Hz, H^2, $H^{2'}$, $H^{2''}$, $H^{2'''}$), 3.81 s (2H, $C^{17}H_2$), 4.65 s (2H, OH×2), 6.89 s (4H, H^{14}, $H^{14'}$, H^{16}, $H^{16'}$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 12.50 (C^{10}, $C^{10'}$, $C^{10''}$, $C^{10'''}$), 20.22 (C^9, $C^{9'}$, $C^{9''}$, $C^{9'''}$), 21.49 (C^8, $C^{8'}$, $C^{8''}$, $C^{8'''}$), 27.57 (C^5, $C^{5'}$, $C^{5''}$, $C^{5'''}$), 33.99 (C^3, $C^{3'}$, $C^{3''}$, $C^{3'''}$), 40.05 (C^6, $C^{6'}$, $C^{6''}$, $C^{6'''}$), 41.86 (C^{17}), 45.46 (C^4, $C^{4'}$, $C^{4''}$, $C^{4'''}$), 46.13 (C^2, $C^{2'}$, $C^{2''}$, $C^{2'''}$), 48.11 (C^7, $C^{7'}$, $C^{7''}$, $C^{7'''}$), 49.84 (C^1, $C^{1'}$, $C^{1''}$, $C^{1'''}$), 125.88 (C^{14}, $C^{14'}$, C^{16}, $C^{16'}$), 128.15 (C^{11}, $C^{11'}$, C^{13}, $C^{13'}$), 132.03 (C^{15}, $C^{15'}$), 152.03 (C^{12}, $C^{12'}$). Found, %: C 85.51, H 10.38. $C_{53}H_{76}O_2$. Calculated, %: C 85.43; H 10.28.

XRD analysis of compound II structure. Single crystals of compound **II** used for X-ray diffraction

study were obtained by slow evaporation of the solution of the compound in chloroform. Thin colorless plate-like crystals, $C_{53}H_{76}O_2 \cdot 2CHCl_3$ (M 983.87), at 100 K monoclinic, a 17.460(6), b 14.153(5), c 21.084(8) Å, α 99.144(6)°, V 5144(3) Å^3, space group $P2_1/n$, Z 4, d_{calc} 1.270 g cm^{-3}. The experimental set of 51333 reflections was obtained on a Bruker SMART APEX2 CCD diffractometer (λMoK_α 0.71073, θ_{max} 27°), using single-crystal sample of size 0.25×0.12×0.03 mm. Processing of the source array of the measured intensities was carried out using SAINT and SADABS software of APEX2 package [11]. The structure was solved by the direct method and refined in full-matrix anisotropic approximation for nonhydrogen atoms with respect to F^2_{hkl}. Hydrogen atoms were placed in geometrically calculated positions, except for the hydroxyl H atoms, whose positions were localized from the maps of the electron density difference. Further, the distance O–H was normalized to 0.85 Å. All hydrogen atoms were refined using the *rider* model. In the refinement were used 11162 independent reflections. The refinement convergence for all independent reflections was wR_2 0.1937 [R_1 0.0861 for 4639 reflections with $I > 2\sigma(I)$]. All calculations were performed using the software package SHELXTL [12]. Atomic coordinates and temperature factors are deposited in the Cambridge Structural Database (no. 873146).

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